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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/027,464	12/20/2001	Sheila J. Kelly	S16.12-0123	1559

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/027,464	KELLY ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-11,17-27 and 41-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,17-27 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 28 February 2007 has been received and entered into the case. Claims 1-5, 10, 11, 23 and 25 have been amended. Claims 6, 7, 12-16 and 28-40 are cancelled. New claims 41-46 have been added. Claims 1-5, 8-11, 17-27 and 41-46 remain pending in the current application, all of which have been examined on the merits.

Response to Arguments

Applicants' arguments of 28 February 2007 have been fully considered. Each argument will be addressed below, as appropriate. Rejections not repeated herein have been withdrawn.

With regards to the rejection of claims 1-5, 9-11 and 16-27 under 35 USC 112, first paragraph, as failing to provide sufficient written description to support the entire genus of elastic proteins, applicants have argued that the specification does provide supporting description for all elastic proteins, by defining elastic proteins as 'mimic[king] the properties of elastin', and because the properties of elastin are known, any engineered protein having properties similar to elastin would also fall within the scope of the claim. Applicants further point out that silk protein, a natural protein, is taught as a suitable elastic protein.

In response, while it is acknowledged that the specification defines elastic proteins as being capable of imparting flexibility to the layer, such as elastin, it remains that applicants have not met the burden of providing a correlation between the recited function (imparting flexibility) and a known or disclosed sequence or common structure. It is only appropriate to define or describe a genus of molecules by a common function or property when there is a known correlation between that property and a sequence (in the case of proteins) or other chemical or physical structure, See *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613. Therefore, without such disclosure applicants cannot be considered to have

possession of the entire genus of proteins which may impart flexibility unto the layers, when only the species of elastin and silk are disclosed.

With regards to the rejection of the claims under 35 USC 102(b) and/or 35 USC 103(a) over Ryan (WO 00/35372), applicants have argued that Ryan does not disclose a reconstituted composition as part of the blood vessel prostheses layers, and thus does not teach each and every limitation of the claimed invention.

In response, it is noted that in accordance with applicants' definition of 'reconstituted composition', each of the layers of the blood vessel prostheses of Ryan are inherently 'reconstituted compositions', as each layer is formed by combining the specified components (both synthetic and purified), and optionally culturing cells on each layer (combining natural tissue fragments), to form a non-natural material for incorporation into the composite. Therefore, the both the inner and outer layer of the blood vessel prostheses of Ryan comprise 'reconstituted compositions' and thus are identical to the claimed subject matter of claim 1. Thus the rejections under 35 USC 102(b), or alternatively under 35 USC 103(a), as set forth below, are deemed appropriate.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 9-11, 17-27 and new claims 41-46 stand/are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It has been held that "an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention... one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process." MPEP § 2163

In the instant application the claims are directed a composite matrix comprising a first layer and a second layer, each layer having a flexibility modifying agent in specified quantities, wherein at least one layer further comprises a reconstituted composition, and wherein the flexibility modifying agent in at least one of the layers comprises an elastic protein.

A question of description arises with the recitation of the genus 'elastic proteins'. Though applicants have argued that their specification has defined elastic proteins as 'proteins that mimic the properties of elastin,' and submit that the properties of elastin are known, it is maintained that such is insufficient to provide written description of the entire genus of elastic proteins. While applicants have identified a function common to all they are considering 'elastic proteins' (said function being mimicry of elastin protein), it has been held that description by functional limitations is only appropriate where there is a disclosed correlation between that particular function *and a structure*; See *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613. Therefore, because applicants have not identified any common sequence (complete or partial) or other chemical or physical properties shared by all elastic proteins, it is not clear that one of ordinary skill in the art would be able to immediately envisage the entire scope of the claimed invention. Therefore, absent any discussion or disclosure of the 'other suitable proteins' which are considered to be 'elastic proteins', there is not considered to be sufficient evidence the applicants were in

possession of the claimed genus of 'elastic proteins', but rather it appears applicants were limited to the single species of elastin, as the only flexibility modifying agent. *See Eli Lilly,* 119F. 3d. at 1568, 43 USPQ2d at 1406. See MPEP § 2163.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8-11, 20-27 and 41-44 stand/are newly rejected under 35 U.S.C. 102(b) as being anticipated by Ryan (WO 00/35372).

Applicant's claims are directed to a composite matrix comprising a first layer and a second layer, each layer having a flexibility modifying agent, the first layer having at least about 5 dry weight percent flexibility modifying agent and the second layer having at least about 5 dry weight percent less flexibility modifying agent than the first layer, wherein at least one layer comprises a reconstituted composition, and wherein the flexibility modifying agent comprises an elastic protein. Some dependent claims further require the first or second layer to further comprise collagen in different concentrations. Some dependent claims further require the flexibility modifying agent to comprise friction reducing macromolecules (examples of such in the specification include hyaluronic acid and chondroitin sulfate, Pg. 23). Some dependent claims limit the thickness of each layer. Some dependent claims require the first or second layers to further comprise cells, growth factors or cell attachment compounds. New dependent claims require the reconstituted composition of the first and/or second layer to comprise a synthetic material or a purified material. New dependent claims require the friction reducing macromolecules of claim 11 to

comprise proteoglycans, specifically chondroitin sulfate, hyaluronic acid and derivatives or mixtures thereof.

Ryan teaches a method of producing a multilayered blood vessel prosthesis by creating and assembling multiple matrices; Ryan further teaches the multilayered blood vessel prostheses thereby produced.

In a preferred embodiment, Ryan teaches a multilayered blood vessel prosthesis that includes (i) an inner layer comprising type I collagen, type IV collagen, GAG, elastin, and laminin (which is inherently a cell attachment compound); and (ii) an outer layer comprising type I collagen, GAG, elastin, and fibronectin (which is also inherently a cell attachment compound) (See Ryan Pg. 3, ln 11-14). Examples of suitable GAGs include chondroitin-6-sulfate, chondroitin-4-sulfate, heparin sulfate, dermatan sulfate, keratin sulfate, chitosan, hyaluronic acid, heparin and combinations thereof (See Ryan, PG. 5, ln 12-16); thus the GAGs included in each layer are considered 'friction reducing macromolecules' in accordance with the definition provided in the specification (pg. 23) (Claims 11, 43 and 44). A third layer can optionally be included between the first and second layers (See Ryan, pg. 3, ln 16-20) (Claim 22). Endothelial cells, smooth muscle cells, and/or fibroblasts can be seeded on one or all of the layers (See Ryan, Pg. 7, ln 9-18) and cultured, after culturing the layers are assembled concentrically to form the final multilayered blood vessel prosthesis, wherein the inner layer forms the inner tube, and the outer layer forms the outer tube. Thus the first and second layers are adjacent, the layers each contain viable cells, and viable cells inherently secrete growth factors (Claims 11, 21, 23-27). Additionally, while not disclosed in the preferred embodiment, Ryan disclose that additional, synthetic biocompatible polymers, such as polyurethanes, can be included in the matrix (See Ryan, pg. 3, line 22-29) (Claim 41). It is further noted that each of the components utilized by Ryan appear to be purified, for example, purified cell populations, purified GAGs, etc (Claim 42). As explained in the "Response to Arguments" section above, each of the layers inherently comprise 'reconstituted compositions' in accordance with the

definition provided by applicants, as each layer is formed by combining the various components (biocompatible polymer matrix, GAGs, elastin, fibronectin, and cells) to form a non-natural composite material.

Ryan teaches each of the matrix layers includes between 50 and 99% collagen; the collagen may be crosslinked to varying degrees depending on the desired mechanical and bioresorptive properties (See Ryan Pg. 8, ln 18-27) (See Ryan, Pg. 8, ln 15-17) (Claims 2-4, 10, 20).

With regards to the elastin content, Ryan teaches each matrix can include up to 30% by weight elastin, preferably between 5 and 20% (See Ryan, Pg. 9, ln 14-16). However, Ryan further teaches that each of the layers/tubes can be manufactured such that the chemical and/or physical compositions are different in each of the tubes, specifically Ryan teaches the inner layer/tube can have a higher concentration of elastin compared to the outer layer/tube (See Ryan Pg. 7, ln 5-9). The instant claims require the second layer to have 'at least about 5 dry weight percent less flexibility modifying agent (elastin) than the first layer', however, because the phrase 'at least about 5 dry weight percent' is not definite, any difference in elastin concentration between the first and second layers is considered to read on the instant claims. Thus, because Ryan teaches an elastin concentration ranging from 5 to 20% in each matrix layer, wherein the inner layer (first layer) has a higher concentration of elastin than the outer layer (second layer), the difference between the elastin concentrations is considered to be 'at least about 5%', and thus the claims are anticipated (Claims 1 and 9). Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-11, 17-27 and 41-46 stand/are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Ryan (WO 00/35372).

Applicant's claims are directed to a composite matrix comprising a first layer and a second layer, each layer having a flexibility modifying agent, the first layer having at least about 5 dry weight percent flexibility modifying agent and the second layer having at least about 5 dry weight percent less flexibility modifying agent than the first layer, wherein at least one layer comprises a reconstituted composition, and wherein the flexibility modifying agent comprises an elastic protein. Some dependent claims further require the first or second layer to further comprise collagen in different concentrations. Some dependent claims further require the flexibility modifying agent to comprise friction reducing macromolecules (examples of such in the specification include hyaluronic acid and chondroitin sulfate, Pg. 23). Some dependent claims limit the thickness of each layer. Some dependent claims require the first or second layers to further comprise cells, growth factors or cell attachment compounds. New dependent claims require the reconstituted composition of the first and/or second layer to comprise a synthetic material or a purified material. New dependent claims require the friction reducing macromolecules of claim 11 to comprise proteoglycans, specifically chondroitin sulfate, hyaluronic acid and derivatives or mixtures thereof. Other new dependent claims limit the concentration of collagen, elastin, and friction reducing macromolecules in the layers.

The teachings of Ryan are set forth above. Ryan anticipates the subject matter of claims 1-4, 8-11, 20-27 and 41-44. With regards to remaining claims 5, 17-19, 45 and 46, the subject matter of these claims would have at least been obvious to one of ordinary skill in the art at the time the invention was made, in view of the teachings of Ryan.

With regards to the type of collagen used in the matrix of each of the layers, it is submitted that though Ryan is silent with regards to the source of the collagen, intestinal collagen would have been an obvious design choice, especially in the absence of evidence showing that the source of the collagen affects the patentability of the final composition (Claim 5).

With regards to the thickness of each of the layers, it is noted that in Example 2, Ryan teach creating individual matrices, which are later used to form the layers, with a thickness of 0.005 inches (127 microns) (See Ryan, Pg. 14, ln 17-18). Therefore, it would have been obvious to one of ordinary skill in the art, in making the product of Ryan, to produce individual layers each with a thickness of approximately 127 microns, which is within the claimed range (Claims 17-19).

Finally, with regards to the concentration of the elastin component, collagen component, and the friction reducing macromolecule component of each of the layers, it is first reiterated that differences in concentration will generally not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical or produces unexpected results. Where the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation, See *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955):

With regards to the concentration (dry wt %) of elastin (flexibility modifying agent) contained in each of the layers, it is noted that Ryan discloses each layer can include up to 30% by weight elastin, preferably between 5 and 20% (See Ryan, Pg. 9, ln 14-16) (Claim 9). However, Ryan further teaches that each of the layers/tubes can be manufactured such that the chemical and/or physical compositions are different in each of the tubes, specifically Ryan teaches the inner layer/tube can have a higher concentration of elastin compared to the outer layer/tube (See Ryan Pg. 7, ln 5-9). Ryan is silent as to the exact difference between the elastin concentrations in each layer; however, he does provide the general teaching that there is to be a difference between the two layers. Therefore, it would have been well within

the purview of one of ordinary skill in the art to optimize the concentration of elastin in each matrix layer, and the corresponding difference between the concentrations, as a matter of routine experimentation.

With regards to the concentration (dry wt %) of collagen contained in each of the layers, it is noted that Ryan discloses a concentration of approximately 50-99% (dry wt) of collagen in each of the matrix layers (See Ryan, Pg. 8, ln 15-17). It is noted this range substantially overlaps with the claimed range of 10-90% (dry wt); it has been held that where the claimed ranges overlap or lie inside ranges disclosed by the prior art a prima facie case of obviousness exists (Claim 46). See *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Finally, with regards to the friction reducing macromolecule component of each of the layers, it is noted that Ryan teaches including GAGs, preferably chondroitin-6-sulfate, at a concentration of between 1% and 10% (dry weight) in each of the matrix (See Ryan, pg 8, ln 15-17). Though this range is slightly lower than that claimed by applicants (about 25% to about 90%) it is noted that Ryan disclose the GAG content directly effects the limit of the resorption rate of the matrix upon implantation; therefore the GAG concentration is a result effective variable, and as such would be routinely optimized by one of ordinary skill in the art without undue experimentation (Claim 45).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B. Lankford, Jr
Primary Examiner
Art Unit 1651